Checkpoint inhibitors in mesothelioma: Hope for the future?

Malignant pleural mesothelioma (MPM) is an aggressive, asbestos-related tumour of the thoracic cavity, with increasing global incidence.[1] Prognosis is poor and treatment options are limited. Pemetrexed/platinum doublet has been standard front-line therapy for non-resectable disease since 2003, when a phase III randomised trial showed a survival benefit of 2.8 months compared with cisplatin alone.[2] Treatment remained unchanged for over a decade, until 2016, when the MAPS trial demonstrated that adding the vascular endothelial growth factor (VEGF) antagonist, bevacizumab, to front-line chemotherapy extended survival to 18.8 months compared with 16.1 for chemotherapy alone.[3] Unfortunately, there is currently no proven second- or third-line treatment for relapsed or progressive MPM, despite significant academic endeavour.

In this context, the publication this month of two promising phase II studies in previously-treated MPM represents important progress. [refs Scherpereel et al, 2018, Disselhorst et al, 2018] Both trials investigated immune checkpoint inhibitors (ICI), used singly or in combination. These agents, which enable perseveration of anti-tumour immune activity by preventing down-regulation of antigen-specific T cells, have yielded impressive results in other poor-prognosis malignancies and recently earned the scientists behind their discovery the Nobel Prize in Medicine. They exert their effect by targeting inhibitory "checkpoint" receptors and their ligands (including programmed death 1 receptor, PD1, and its ligand, PDL1), preventing interactions that would otherwise lead to apoptosis of effector T cells and maintenance of regulatory T cells. This approach is of interest in MPM - a tumour that can co-opt inhibitory pathways by expressing PDL1, and thus may be vulnerable to checkpoint blockade.

Reported in this journal, the IFCT-1501 MAPS2 trial saw the Intergroupe Francophone de Cancérologie Thoracique randomly allocate 125 patients to receive nivolumab (a PD1 inhibitor) alone or in combination with ipilimumab (an ICI targeting cytotoxic-T-lymphocyte 4 (CTLA4)) until disease progression or unacceptable toxicity occurred.[ref scherpereel et al, 2018] Patients were of good performance status, with histologically-proven, non-resectable MPM that had progressed radiologically following at least one line of standard-agent chemotherapy. This well-organised French research collaborative should be congratulated on the rapidity of recruitment, which was completed within 5 months.

The primary aim was to report 12-week disease control rates (DCR - defined as complete response, partial response or stable disease) in the initial 108 eligible participants. The intention was not to compare the two regimens, and the study was not powered to do so, but rather to describe the efficacy and tolerability in each arm, with a view to designing a subsequent comparative phase III trial. To this end, the authors report DCR of 44% in the nivolumab arm and 50% in the combination arm. Secondary analyses revealed progression-free survival (PFS) of 4 months and 5.6 months, median overall survival (MOS) of 11.9 months and 15.9 months, and 1-year survival rates of 49% and 58%, in nivolumab and nivolumab/ipilimumab arms respectively.

In the second trial, INITIATE, published this month in Lancet Respiratory, Dr Disseldorf and colleagues treated 34 patients with combination ipilimumab and nivolumab for up to 2 years, or until disease progression or unacceptable toxicity.[ref Disselhorst et al, 2018] Patients had received at least 1 cycle of platinum-based chemotherapy, with several patients receiving multiple lines of treatment, including some experimental agents. 12-week DCR (the primary outcome) was 68%, with a median duration of response of 14.3 months. MOS was not reached but was estimated, with 95% confidence, to exceed 12.7 months. The 1-year survival rate was 64%.

From these data, ICI appear more efficacious than second-line chemotherapy, which is associated, at best, with PFS of 3.8 months and MOS of 10.5 months.[4] The results reinforce other early-phase studies of ICI in MPM, including the non-randomised NivoMes trial, which demonstrated DCR of 47% and 1-year survival rates of 50% in MPM patients treated with single-agent nivolumab.[5] Combination nivolumab and ipilimumab has not been studied in MPM before, but an alternative PD1/CTLA4 combination, durvalumab and tremelimumab, was used in the NIBIT-meso-1 trial. 40 patients were treated, in the first or second-line setting, of whom 23 (63%) demonstrated disease control, with a PFS of 5·7 months and MOS of 16·6 months.[6]

The drugs are not without side effects, however, especially when used in combination. Over 93% of patients who received nivolumab and ipilimumab in either study experienced an adverse event (AE), with 26% and 34% of participants in MAPS2 and INITIATE, respectively, experiencing at least one treatment-related AE of grade 3-4 severity. Additionally, there were 3 (4.8%) treatment-related deaths in the combination arm of MAPS2, and 21% of patients discontinued treatment due to side effects. Nivolumab monotherapy appeared less toxic with 14% of recipients experiencing a grade 3 or 4 AE, and no treatment-related deaths. In keeping with previous experience, the most common AE were fatigue, diarrhoea and anorexia, with acute kidney injury and derangement of liver enzymes the most important haematological events. Perspective is required, however. Chemotherapy is associated with much higher complication rates, with 44% of patients treated with pemetrexed and cisplatin experiencing grade 3 or 4 neutropaenia in a previous trial, and over 75% some degree of nausea and vomiting.[3] As with all treatments, the deciding factor will be whether clinicians and patients consider the risk of side effects to be outweighed by potential benefit, a decision that is likely to vary between individuals.

These two trials inspire optimism for several reasons. Firstly, the rapidity of recruitment in a sub-population of patients with a rare disease is impressive. Improved public engagement, patient involvement in trial design, and wider dissemination of results has led to increased awareness of research amongst MPM patients, carers and other stakeholders. This a welcome development and, as researchers, we must respond by ensuring our patients have optimal and equitable access to MPM studies, both for their benefit and to expedite further therapeutic advances.

Secondly, the trial results are encouraging, and their consistency with each other and existing data suggests they are reliable. However, we must be mindful of the limitations of non-comparative trials, including selection bias and, in the post-front-line setting, survivorship bias. External validity is also unverified, as participants were of good performance status, and both studies excluded patients

with certain poor-prognostic indicators (i.e. weight loss, uncontrolled chest pain). Above all, history has taught us that promising phase II data is no guarantee of demonstrable efficacy in suitable-powered randomised trials. This was exemplified, pertinently, in two recent tremelimumab studies, MESOT-TREM and DETERMINE. In the initial single-arm study, tremelimumab produced DCR of 52% in 29 pre-treated patients with mesothelioma, but the subsequent randomised, double-blind, placebo-controlled trial of 569 patients showed no difference in survival between patients given tremelimumab versus placebo.[8,9]

Well-designed phase III trials are required, therefore, to evaluate the clinical efficacy of ICI in the second- and third-line setting. Several studies are underway investigating single-agent PD1 inhibitors in this context, including pembrolizumab in PROMISE (NCT02991482) and nivolumab in CONFIRM (NCT03063450). Phase III trials of combination ICI in this setting are awaited, although CheckMate BMS CA209-743 (NCT 02899299) is evaluating combination nivolumab/ipilimumab in front-line patients, in direct comparison with standard chemotherapy.

Phase III trials will also enable clarification of ongoing areas of uncertainty. Of particular interest is the role of tumour PDL1 expression in predicting treatment response, as well as the most sensitive assay with which to measure it and the optimal threshold to determine high or low expression. Larger trials will also enable exploration and further quantification of "hyper-progressors" – an important phenomenon that is currently poorly understood. This information could facilitate a move towards personalised treatment for MPM, with the potential to improve outcomes and enhance patients' experiences.

In summary, the publication of these two promising studies represents an important and encouraging advance for MPM. ICI have made an enormous impact on the treatment of other poor-prognosis malignancies, such as melanoma and non-small cell lung cancer. It is possible they may do the same for MPM, in time, however, for now we must temper our enthusiasm and direct all efforts toward supporting definitive trials, for it is these that have the potential to transform the treatment landscape of MPM.

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